

## **SUNITINIB INDUCED HYPOTHYROIDISM → IS THYROID FUNCTION TEST NEEDED PRE-OPERATIVELY**

### **ABSTRACT**

Reported is a case of intra-operative management of a patient with recurrent renal cell carcinoma for partial nephrectomy with a chance diagnosis of hypothyroidism along-with abnormal thyroid function test. Sunitinib was identified as the causative agent. The mechanism of action as well as the side effects of sunitinib are also described. The use of levothyroxine via the Ryle's tube in the event of non-availability of intravenous T3 or T4 is also stressed upon. On the basis of retrospective and prospective studies the need of monitoring the thyroid function in patients on sunitinib is now clearly emphasized.

**Key words:** Hypothyroidism, Sunitinib, l-thyroxin

### **INTRODUCTION**

Kidney cancer is in a rise worldwide during the past few years. Sunitinib is an oral, multi-targeted tyrosine kinase receptor inhibitor approved by FDA for the treatment of metastatic renal cell carcinoma(RCC).<sup>1</sup> Apart from the common adverse effects of sunitinib therapy like fatigue, diarrhoea, nausea, anorexia, hypertension, hand foot skin reaction and stomatitis, hypothyroidism and reversible erythrocytosis have also been associated.<sup>2</sup> We report the anaesthetic management of incidental hypothyroidism attributed to sunitinib chemotherapy in a case of RCC scheduled for salvage surgery for tumour recurrence.

### **Case report**

A 53 years old, 77 kilogram, diabetic male, diagnosed case of Recurrent Renal Cell Carcinoma was posted for redo right partial nephrectomy with adrenalectomy. He had earlier undergone left radical nephrectomy, right partial nephrectomy and Radiofrequency Ablation of recurrence in remnant right kidney. He had also received External Beam Radiotherapy for the same disease. In view of repeated recurrences and only about half a kidney remaining, he was started on Tab Sutent (SUNITINIB) 50 milligram (mg) once daily to slow the progress of the disease. As he developed another recurrence in the remaining kidney he was posted for surgery in an attempt to salvage some renal tissue. He was also a recently diagnosed diabetic on treatment with oral hypoglycemic agent. There was no other positive medical or drug history which could be attributed to any previous thyroid dysfunction.

On examination, he had a yellowish discoloration of the skin. Other biochemical investigations revealed a mild thrombocytopenia (1,21,000/cubic mm), marginal derangement of renal function with serum creatinine = 1.6 mg % (due to only half a kidney remaining), some degree of hyponatremia (serum Na<sup>+</sup> = 130meq/L). ECG showed a borderline AV conduction delay but the 2D echocardiography was normal. Hyponatremia was corrected prior to the surgery.

On the day of surgery the patient received an oral premedication of Tablet (Tab) Alprazolam 0.25 mg, Tab Granisetron 2 mg and Tab Ranitidine 150 mg on the morning of surgery.

Anaesthesia was induced with a hypnotic dose of propofol and atracurium as the non depolarizing muscle relaxant. Opioids in the form of Morphine and Fentanyl were used but in reduced doses due to compromised renal function. Anaesthesia was maintained with O<sub>2</sub>:N<sub>2</sub>O (50:50) with Isoflurane and Atracurium top ups guided by neuromuscular monitoring. Fentanyl boluses were given as and when hemodynamic response occurred. A total of 4.5 mg morphine and 200 microgram (mcg) of Fentanyl (approximately 2.5mcg/kg) was given over the total duration of the surgery (2.5hours).

Sample for thyroid function had been sent by the surgical team to monitor any hypothyroidism due to Sutent therapy. The anaesthesia team was unaware of such a side effect of the drug. In between the surgery a report of thyroid function was received which showed a TSH value of 166 uIU/ml (0.468 -4.68 uIU/ml), T3 -4.91 pg/L (4.26-8.10 pg/L), T4 -4.76 pg/L (10-28.2 pg/L). When we received the report, further use of narcotics was immediately discontinued.

An entropy sensor was attached to monitor the depth of anaesthesia. Patient was switched over to O<sub>2</sub>:Air mixture along-with sevoflurane for preventing any delayed recovery at the end of the procedure. After consultation with an endocrinologist Tab Thyroxin 200 mcg was given through the Ryles tube. A patient warming blanket (Bair Hugger) and a fluid warming system were being used from the beginning of the surgery, as a routine, in all major cases which took care to prevent any hypothermia.

As the patient underwent Adrenalectomy along-with nephrectomy, he was given steroid supplementation in the form of Inj. Hydrocortisone 100 mg IV bolus followed by an infusion at the rate of 5mg/hr. This infusion was continued in the post operative period till he started accepting orally. At the end of the surgery, the patient had an uneventful recovery. In the post operative ward special care was taken to prevent hypothermia. Tab Thyroxin was continued at 100 mcg once daily along with steroid supplementation as mentioned above. His blood sugar levels were monitored and corrected by giving Insulin. He was discharged from the post-operative ward on the 4<sup>th</sup> post-operative day.

## DISCUSSION

Anticancer chemotherapeutic drugs have a vast array of adverse effects. We are aware of a few of them like cardiac toxicity of Anthracyclines (Adriamycin, Epirubicin), pulmonary toxicity of Bleomycin, neuropathy due to Cisplatin and bone marrow suppression due to almost all the chemotherapeutics<sup>3</sup>. These generalized and organ specific toxicities may give rise to various unpredictable life-threatening per-operative complications.

Sunitinib is a newly introduced oral chemotherapeutic drug approved by FDA in 2006 for the treatment of metastatic renal cell carcinoma and Imatinib resistant gastrointestinal stromal tumor.<sup>4</sup> It is a multi-targeted receptor Tyrosine kinase inhibitor. These include all receptors for platelet derived growth factor and vascular endothelial growth factor receptors. The fact that sunitinib targets many different receptors, leads to many of its side effects such as the classic hand-foot syndrome, stomatitis and other dermatologic toxicities. The most common adverse side effects associated with sunitinib therapy are – fatigue, diarrhea, nausea, anorexia, hypertension, a yellow discoloration of skin, hand – foot skin reaction and stomatitis. Laboratory abnormalities include fall in lipase, amylase, neutrophils, lymphocytes and platelets. Signs and symptoms of sunitinib toxicity such as fatigue, weakness and depression may be attributed erroneously to cancer itself thus delaying the diagnosis of hypothyroidism. The first reported case in the literature of myxedema coma induced by sunitinib was published in 2009.<sup>5</sup> Close vigilance is therefore needed.

Hypothyroidism has also been associated with sunitinib. In a prospective study, Wolter et al found a 27 % incidence of sub clinical or clinical hypothyroidism in a study group of 56 patients<sup>6</sup>. In other retrospective studies the incidence of hypothyroidism has been placed at 53-85 %.<sup>7</sup> According to Naranjo ADR probability scale-items and score, there was a definite association between sunitinib and hypothyroidism.<sup>8</sup> There are other drugs like Radioiodine, Amiodarone, Lithium and Phenytoin which are known to cause hypothyroidism in patients treated with them.<sup>9</sup> As a result, thyroid functions are monitored periodically in patients on therapy with these drugs. The same should be followed with sunitinib and thyroxine supplementation given as required.

It is known that the anaesthetic requirement is decreased in patients with hypothyroidism. There is no practical index by which we can estimate the optimal dose of anaesthetic agents for these patients. Assessment of the hypnotic level by bispectral index can be utilized as

an efficient index to determine the optimal dose of general anaesthetics for patients with hypothyroidism.<sup>10</sup> In our case, we used entropy as a guide to the depth of anaesthesia after we received the report of TSH. It also helped us to facilitate decrease in the total dose of opioids and volatile agents, thus preventing delayed recovery at the conclusion of the surgery.

The available literature on thyroid hormone replacement therapy in patients with myxedema coma comprises of three categories IV T4, oral T3 or IV T3. Due to the low availability of IV T4 in our country, oral T4 in the form of Tab. Thyroxin was given through the ryles tube. It has been found by some investigators that oral administration of L-T4 is associated with variable but quick response even in patients with myxoedema ileus.<sup>11</sup>

There have been other case reports of treatment of cases of myxoedema coma with nasogastric or IV administration of triiodothyronine.<sup>12</sup> It is highly advisable to treat myxoedematous patients with levothyroxin before elective surgery. In an emergency, treatment should consist of levothyroxin sodium 500mcgIV, by nasogastric tube or orally.

Due to associated glucocorticoid deficiency in patients with long standing hypothyroidism, a glucocorticoid support is indicated in the form of an IV bolus of 100mg Hydrocortisone followed by an infusion @ 4mg/hr. Hypothermia is another problem in hypothyroid patients presenting for surgery. We recommend routine use of patient warmers, fluid warmers and use of warm saline by the surgical team for giving intra-abdominal washes.

In conclusion, effects of tyrosine kinase inhibitors on thyroid hormone metabolism should be well-known to the anaesthesiologists working in cancer hospitals. It is recommended that thyroid functions tests should be routinely monitored in patients on sunitinib therapy and their euthyroid status be confirmed prior to surgery. Also in an emergency, Thyroxin can be administered via Ryles tube to tide over such a crisis.

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